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Review

Review of Potential Diagnostic and Therapeutic Developments in Systemic Lupus Erythematosus (SLE)

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Abstract

Systemic lupus erythematosus (SLE), a complex autoimmune disease, affects multiple tissues and organs, presenting substantial challenges for both diagnosis and treatment. Both innate and adaptive immune cells are involved in the intricate pathophysiology of SLE. The characteristics of SLE include the production of autoantibodies and the formation of immune complexes that accumulate within the vasculature, leading to organ damage. Although progress in understanding the pathogenesis of SLE has lagged behind that of other autoimmune rheumatic diseases, recent findings have highlighted promising therapeutic targets and raised the prospect of personalized treatment strategies. This narrative review was conducted through a comprehensive analysis of recent literature focused on the pathogenesis, diagnosis, and treatment of SLE. Prospective experimental and clinical studies with well-documented results were selected for analysis. Diagnostic biomarkers were evaluated for their sensitivity, specificity, and correlation with disease activity indices, such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Therapeutic agents, including monoclonal antibodies, interferon, and interleukin inhibitors, as well as emerging small molecules, were assessed based on clinical trial outcomes and potential future applicability in clinical practice. Several promising biomarkers, such as pentraxin 3 (PTX3), S100 calcium-binding protein A8 (S100A8), B cell differentiation factor (BCDF), interferon gamma-induced protein 10 (IP-10), urinary activated leukocyte cell adhesion molecule (ALCAM), vascular cell adhesion molecule 1 (VCAM-1), and platelet factor 4 (PF4), have shown strong correlations with disease activity and lupus nephritis (LN). Among treatments, monoclonal antibodies, such as belimumab and anifrolumab, are already approved by the United States Food and Drug Administration. Meanwhile, others, including obinutuzumab and sifalimumab, have demonstrated encouraging results in Phase II trials. These developments reflect growing potential for precision diagnostics and targeted therapy in SLE. Recent advances in understanding the immunological underpinnings of SLE have led to the identification of sensitive and specific biomarkers, as well as novel biologics, which may overcome the limitations of traditional therapies. Biomarkers such as PTX3 and S100A8 can facilitate early diagnosis and may also predict treatment efficacy, offering the foundation for tailored therapeutic strategies. The continued evaluation of emerging biologics, particularly those targeting B cells and the interferon pathway, holds promise for enhancing disease management and improving long-term patient outcomes.

Keywords: SLE; systemic lupus erythematosus; diagnostics; monoclonal antibodies

1. Introduction

Relapsing and remitting phases are hallmarks of systemic lupus erythematosus (SLE), an autoimmune disorder that can severely damage numerous organs. The kidneys, joints, nervous system, and skin are the organs most commonly impacted by SLE. The characteristics of SLE include the generation of circulating autoantibodies and the development of immune complexes that accumulate in the arteries. These complexes trigger potent inflammatory reactions, resulting in damage to multiple organs [1]. In all regions, the incidence and prevalence of SLE have risen in recent decades. According to current estimates, the total incidence of SLE varies by geographic region, ranging from 0.3 to 23.2 cases per 100,000 individuals [2]. North America has the highest occurrence, whereas sub-Saharan Africa, Europe, and Australia have reduced incidences. Different genetic predispositions, in addition to socioeconomic and environmental factors, contribute to these variations. Women of reproductive age are more susceptible to SLE compared to men, with an incidence ratio that ranges from 8:1 to 15:1 [2].

From an immunological perspective, SLE arises from a breakdown of self-tolerance and sustained activation of both innate and adaptive immune responses. Genetic and epigenetic factors, as well as environmental exposures, such as ultraviolet radiation and infections, have been implicated in the initiation and perpetuation of disease [3]. Numerous studies have identified abnormalities in B and T lymphocyte function, type I interferon signaling, dendritic cell activation, and neutrophil extracellular trap formation as key drivers of disease pathogenesis [4,5].

The presence of clinical signs, such as neuropsychiatric symptoms, glomerulonephritis, joint pain, and eczema, and laboratory test results are currently the main factors used to diagnose lupus. Nevertheless, the laboratory indicators presently available for SLE diagnosis are not ideal. For example, the antinuclear antibody (ANA) test has a relatively low specificity of 61% and a high general sensitivity of 94%. Conversely, double-stranded DNA antibodies exhibit strong specificity for the detection of SLE; however, these antibodies have limited sensitivity due to their transient nature [6]. Thus, predicting the future course of the disease and regularly assessing and monitoring the disease progression are essential for improving therapy outcomes. Recent international guidelines emphasize the need for more accurate biomarkers for diagnosis and disease monitoring [7], particularly those that can reflect organ-specific activity and therapeutic response. Additionally, more precise and trustworthy biomarkers for SLE are needed to track the course of the illness, evaluate the effectiveness of treatment, and predict upcoming exacerbations.

The objectives for SLE treatment include optimizing symptom control and disease remission, enhancing long-term patient outcomes, preventing end-organ damage, and improving the quality of life of the patient. Therefore, antimalarials, of which hydroxychloroquine is the most widely used, are the first class of medications for the maintenance phase of SLE. Depending on the severity of the illness, intravenous prednisolone may be administered in acute phases before being gradually lowered and replaced with immunosuppressive drugs or an antimalarial medication [8]. Glucocorticoids are typically administered during disease flare-ups to promote remission by gradually reducing the dosage and then switching to an immunosuppressant or hydroxychloroquine. However, the need to develop novel treatment techniques arises from adverse effects, relapses, exacerbations, and damage to target organs [9].

Over the last decade, rapid progress has been made in identifying novel serological and urine biomarkers, such as cytokines (e.g., interleukin (IL)-17, IL-6, interferon (IFN)-α), chemokines (e.g., interferon gamma-induced protein 10 (IP-10)), S100 calcium-binding protein A8 (S100A8)/A9 proteins, and adhesion molecules (e.g., vascular cell adhesion molecule 1 (VCAM-1), activated leukocyte cell adhesion molecule (ALCAM)), which have been proposed for diagnosis and monitoring of SLE activity and complications, particularly lupus nephritis (LN). Simultaneously, the therapeutic landscape is evolving toward biological and targeted therapies, with monoclonal antibodies such as belimumab and anifrolumab already approved for clinical use and others under investigation in various stages of clinical trials [10,11].

Therefore, this review aimed to provide a comprehensive synthesis of recent advances in the discovery of diagnostic and prognostic biomarkers, as well as the development of novel therapeutic agents. Particular attention is provided to biomarkers that demonstrate organ specificity, clinical relevance, and potential for implementation in routine practice, as well as to biological therapies that target key immune pathways implicated in disease progression. By integrating recent evidence from both experimental and clinical studies, this review aims to highlight the most promising directions for improving early diagnosis, individualized monitoring, and therapeutic outcomes in patients with SLE.

2. General Pathogenesis of SLE

2.1 The Role of Adaptive Immunity

The B cell receptor (BCR) is expressed on the surface of B cells, a distinguishing characteristic of these cells. The physiological makeup of the receptor enables the receptor to identify infections and then generate specific antibodies in response. However, autoreactive B cells can also arise during the development of B cells. Meanwhile, immunological tolerance mechanisms, such as clonal deletion or peripheral anergy induction, regulate the progression of these host-threatening cells, but can sometimes fail. Thus, autoimmune disorders may develop due to the unintended growth and activation of these autoreactive B cells [12]. Soluble factors are necessary for the survival and proliferation of B cells, particularly once autoreactive B cells have formed. The B cell-activating factor (BAFF), also known as B lymphocyte stimulator (BLyS), is the most significant of these [13]. The repertoire of autoantibodies produced by autoreactive B cells mostly targets nuclear antigens. The majority of these autoantibodies are generated by toll-like receptors (TLRs). TLR7 and TLR9 subtypes interact incorrectly in SLE, effectively stimulating the production of autoantibodies against double-stranded DNA and RNA-associated autoantigens [14]. In SLE, long-lived plasma cells (LLPCs), which are produced after B cells terminally differentiate, are a significant source of autoantibodies. Short-lived plasmablasts have been shown to transform into high-affinity plasma cells that move to specific bone marrow locations after engaging with $CD4^+$ lymphocytes in the germinal centers of lymph nodes. There, these short-lived plasmablasts are shielded from the environment, have a long lifespan, and can continue to make autoantibodies. For murine and human SLE pathogenesis, spontaneous germinal center formation, which stimulates the creation of duodenal cells, has been observed, indicating that this event is solely related to the genesis of autoantibody synthesis [15].

The development of SLE is significantly influenced by autoreactive T cells, which promote oxidative stress associated with the generation of IFN-γ. Meanwhile, T helper 1 (Th1) lymphocytes play a crucial role in the pathophysiology of SLE [15]. Conversely, the peripheral blood of SLE patients contains fewer IL-4-producing Th2 cells, which may indicate their protective function and suggest that SLE activity is linked to a higher IFN-γ/IL-4 balance. The pathogenesis of SLE also involves T helper 17 (Th17) cells,

which are the primary sources of IL-17, a cytokine with potent inflammatory effects. Members of the IL-17 family can exacerbate tissue damage due to their proinflammatory activity, which also activates the innate immune system, recruits neutrophils, and enhances B lymphocyte function [16]. Peripheral tolerance to autoantigens is largely maintained by regulatory T cells, also known as Tregs. Despite descriptions of both quantitative and qualitative variations in Tregs in SLE patients, research to date has yielded contradictory findings, and the role of Tregs in SLE remains unclear. Both extrafollicular foci and germinal centers contain T follicular helper cells (Tfh). In both humans and mice with SLE, these cells have been linked to the production of autoreactive B cell clones [17]. Tfh cells have been seen to cluster alongside B cells in tissue from the renal tract. When considered as a whole, these findings support the notion that interactions between $CD4^+$ lymphocytes and B cells are essential for the progression of autoimmunity, as these interactions play a crucial role in the development of autoreactive B cells. These autoreactive B cells subsequently mature into plasma cells, which generate autoantibodies. Furthermore, $CD8^+$ T cells play a role in the pathogenesis of SLE. The circulating $CD8^+$ T cells in SLE patients exhibit functional abnormalities, including decreased granzyme and perforin generation, as well as compromised cytolytic activity [18].

2.2 The Role of Innate Immunity

It has been noted that neutrophil function is abnormal at several levels in SLE. First, neutrophils exhibit reduced phagocytic capacity and failure to clear apoptotic cells, which are a known source of normally occult autoantigens [19]. Variants in the *ITGAM*, *NCF1*, and *NCF2* genes have been identified as risk factors for the development of SLE, as these variants lead to altered phagocytosis and dysregulation of reactive oxygen species (ROS) production [20]. It has also been reported that neutrophils can produce type I IFN independent of TLR stimulation and promote abnormal B cell development in the bone marrow of SLE patients. A neutrophil subtype, known as low-density granulocytes (LDGs), is highly represented in the peripheral blood of patients with SLE. These cells are associated with the presence of the IFN signature and disease severity and activate $CD4^+$ T cells to produce IFN-γ and tumor necrosis factor alpha (TNFα) [21]. In SLE, neutrophils are characterized by an increased ability to form neutrophil extracellular traps (NETs), which are released during apoptosis. NETs are rich in decondensed nucleic acids, and the chromatin displaced outside the cells during the formation process can induce specific autoreactive immune responses against nucleic acid antigens [22].

Lymphoid-derived plasmatocytoid dendritic cells (pDCs) are important in the pathophysiology of SLE because of the capacity of these cells to generate large amounts of type I IFN. Connecting innate and adaptive immunity also requires PDC-dependent IFN type I production, which is promoted by complex interactions between monocytes, neutrophils, T and B cells, and natural killer cells [23]. Proinflammatory T cell recruitment and numbers are also increased by PDC activation and elevated IFN-I production; this predominantly occurs at the arterial wall. Accelerated atherosclerosis, commonly observed in SLE, has been linked to this finding [24].

2.3 The Role of Mitochondria

Mitochondria are organelles that supply energy for cell metabolism and survival and are the primary source of adenosine triphosphate (ATP) generation. After being destroyed by cell apoptosis, these ancestral structures can release mitochondrial DNA (mtDNA). However, mtDNA is extremely instability and easily degraded, leading to the production of antigenic fragments [14]. Meanwhile, mtDNA has been shown to activate certain autoreactive T cells in patients with SLE. Subsequently, B cells may then develop antibodies against the DNA. Additionally, mtDNA sequences have been noted to trigger TLRs because these sequences resemble those of bacteria. Strong downstream inflammatory reactions, such as the generation of type I IFN, are triggered by TLR detection. This proinflammatory reaction further exacerbates the collapse of tolerance. Several mitochondrial gene variants have also been reported to be associated with the risk of developing SLE, as demonstrated in mouse models [25].

3. New Diagnostic Developments for SLE

3.1 Cytokines

Cytokines play an important role in the pathophysiology and immunology of SLE. Therefore, several promising cytokines have been investigated as diagnostic or prognostic biomarkers of SLE. According to prior research [26], SLE patients exhibited higher levels of the following cytokines compared to healthy study participants: IL-8, granulocyte-colony stimulating factor (G-CSF), IL-12/23p40, IFN-α, TNFα, IL-17A, IL-6, and IL-10. Another study found that SLE patients had much greater levels of IL-17, IL-6, and high-sensitivity C-reactive protein (hsCRP) compared to normal volunteers, and that these levels were directly correlated with the severity of the condition [27].

Pentraxin 3 (PTX3) contributes to the dysregulated immune response in SLE by modulating innate immunity, complement activity, leukocyte trafficking, and autoantigen persistence, all of which are central to the pathogenesis of the disease [21]. It has been shown to correlate with disease activity and vascular damage in SLE patients. The cutoff value was 2.8 ng/mL, with a sensitivity of 100% and a specificity of 80% for plasma PTX3, which was substantially greater in SLE patients than in healthy people [27].

B cell differentiation factor (BCDF) is essential for B lymphocyte proliferation, and SLE patients have higher lev-

els of BCDF than control subjects. With an 80.6% sensitivity and a 70.8% specificity, receiver operating characteristic (ROC) analysis revealed that BCDF had an area under the curve (AUC) of 0.861 in separating patients with SLE from healthy people [28].

Cysteine-rich angiogenic inducer 61 (Cyr61), also known as CCN1, is a matricellular protein that plays an active role in inflammation, tissue remodeling, and vascular biology—all of which are relevant to the pathogenesis of SLE [29]. In SLE, Cyr61 is overexpressed and correlates with disease activity, particularly in patients with active LN. Patients with SLE had higher serum levels of Cyr61 than healthy individuals; ROC analysis suggested that Cyr61 may be a useful predictor of SLE prognosis. Compared to healthy individuals, SLE patients had increased levels of plasma growth arrest-specific protein (Gas6), with a sensitivity of 47% [29].

3.2 Chemokines

The family of small (8–10 kDa) chemoattractant cytokines, known as chemokines, controls the migration and localization of immune cells. In both murine and human models, chemokines and their corresponding receptors have been demonstrated to play a crucial role in the pathophysiology of SLE. Moreover, certain chemokines have been shown to be highly effective indicators for predicting and diagnosing SLE, with a sensitivity of 76% and a specificity of 70%; meanwhile, serum IP-10 may also help distinguish SLE from healthy individuals [30].

3.3 S100A8

During the inflammatory response, neutrophils release S100A8, a Ca^{2+} binding protein that is a member of the S100 family, as part of their extracellular traps [31]. S100A8 is mostly recognized in the S100A8/A9 heterodimer, but it also functions as an injury-associated molecular pattern and builds up in the blood and other body compartments following release. This is because S100A8 is a crucial regulator of inflammation that activates innate immune cell activity by interacting with participants of the immunoglobulin superfamily of cell surface molecules, specifically TLR4 and advanced glycation end product receptor. Serum S100A8 concentration has been found to be higher in patients with SLE than in healthy controls (HCs), and it has been linked to glomerulonephritis, anti-double-stranded DNA antibodies, and disease activity, according to growing experimental and clinical data [32]. The diagnostic efficacy of S100A8 for SLE was evaluated in a study [33]. SLE patients have been shown to exhibit significantly higher mean levels of S100A8 in their serum, urine, and saliva compared to patients with chronic gingivitis (CG). Although no prior research has used the S100A8 homodimer to compare SLE patients with CG patients, a study of 37 SLE patients revealed a significant decrease in serum S100A8 levels following treatment [33].

Although salivary S100A8 has been considered a potential diagnostic biomarker for oral cancer or infection, there is currently no information available regarding the expression of S100 protein in the saliva of SLE patients [34]. S100A8/A9 has been identified as a biomarker for Sjögren's syndrome, a condition that primarily affects the exocrine glands, particularly the salivary and lacrimal glands [35]. Additionally, it was discovered that patients with inflammatory bowel illness and systemic sclerosis had higher salivary S100A8/A9 levels than people with a germinal center (GC). According to a study, patients with SLE had considerably greater salivary S100A8 concentrations than those with GC, and these concentrations were correlated with clinical indicators of disease activity, such as anti-double-stranded DNA antibodies and erythrocyte sedimentation rate (ESR) [36].

3.4 ALCAM, VCAM-1, and PF4

ALCAM (also known as cluster of differentiation 166, or CD166) is a cell adhesion glycoprotein that is extensively expressed on antigen-presenting cells and is essential for leukocyte activation and recruitment, as well as T lymphocyte costimulation. ALCAM has been shown to function as a diagnostic marker of inflammation, angiogenesis, and treatment responsiveness in various malignancies [37]. Serum ALCAM levels and renal tissue expression were markedly elevated in diabetic nephropathy, with glomeruli and tubules exhibiting upregulated ALCAM expression. In recent high-throughput proteomic approaches, urinary ALCAM has shown promising results in predicting LN activity in SLE patients [38]. Further testing in SLE patients confirmed higher urinary ALCAM levels with significant correlation with total and renal SLEDAI scores [39].

VCAM-1, also known as CD106, is a widely expressed cell adhesion molecule in the peripheral circulation, primarily expressed in endothelial cells and glomerular parietal epithelial cells. One of the study studies has shown elevated and highly correlated serum and urinary VCAM-1 levels with LN activity and severity [40]. Additionally, some research has documented both a decrease in VCAM-1 following treatment and a correlation with proliferative subtypes of LN [41].

Platelet factor 4 (PF4), an antiangiogenic chemokine that regulates angiogenesis through an integrin-dependent mechanism, is another prospective biomarker for SLE and LN. PF4 stimulates profibrotic cytokines, such as IL-4 and IL-13, and inhibits antifibrotic cytokines (interferon-γ). Additionally, PF4 promotes the development of Tregs [42]. Furthermore, the functions of PF4 in atherosclerosis, cancer, and heparin-induced thrombocytopenia are well known. Furthermore, higher serum PF4 levels have been presented in patients with antiphospholipid syndrome and those with systemic sclerosis [43]. Urinary PF4 has been validated in recent publications as a viable biomarker to distinguish between adult patients with active LN and is as-

sociated with changes in biopsy activity. Consistent with these results, the present investigation demonstrated that, compared to other SLE categories and controls, patients with active LN had the highest urine PF4 levels [44]. A comparison of the markers described above is presented in Table 1 (Ref. [26–30,32,33,38–41,44]).

The most promising markers are those whose levels correlate with the severity of the disease, such as the SLEDAI index, which has high sensitivity and specificity indicators. According to these indicators, the best option based on the above analysis is the PTX3 protein. It is also worth paying attention to biomarkers that have a high correlation with the development of LN. The S100A8 biomarker holds great promise, as this biomarker also enables the diagnosis of therapy effectiveness. The development of test systems that assess the prospects of treatment can be a great help in the fight against SLE.

4. Potential Therapeutic Developments for the Treatment of SLE

4.1 Targeted Treatment of B cells

The involvement of B cells is a hallmark of the pathogenesis of SLE [39]. As a result, several treatment approaches targeting B cells have been employed [45,46]. SLE develops autoantibodies through various processes, including the activation of cytokine and interferon production by innate immune lymphocytes, which contribute to the inflammatory response. Patients with SLE have compromised immunological mechanisms, which are further compromised by aberrant immune cell activity [47]. There are already or will soon be new treatments that target B cells. Treatment focuses on substances that contribute to the development, activation, or proliferation of B cells. Furthermore, B cell subgroups have been shown to express certain molecules that, when targeted, can cause their anergy, apoptosis, and depletion [48].

Rituximab is an anti-CD20 monoclonal antibody that depletes B cells and is utilized as a targeted treatment of B cell-related disorders. Since stem cells and plasma cells do not express the CD20 molecule, rituximab spares these cells while depleting CD20-positive B cells. Rituximab cytotoxically destroys B lymphocytes through complement-mediated and antibody-dependent mechanisms. Moreover, rituximab cytotoxically decreases proliferation and triggers B cell death. Refractory SLE with neuropsychiatric and renal symptoms may be treated with rituximab [49]. According to a thorough analysis, rituximab significantly reduces systemic symptoms in more than 90% of patients with lupus. Since several trials failed to fulfill their primary goals, the United States Food and Drug Administration (FDA) has yet to authorize rituximab for the treatment of SLE. Randomized controlled trials, as well as the EXPLORER and Lupus Nephritis Assessment studies, have assessed the efficacy of rituximab in treating SLE. Rituximab has been shown to be safe and efficacious in non-renal SLE and efficacious in refractory neuropsychiatric SLE [50]. Rituximab lowers immunological markers and disease activity, while also helping to reduce steroid dose. Rituximab can also be used to treat thrombocytopenia and arthritis. Rituximab has been demonstrated to be beneficial in treating renal failure in patients with lupus. Since early B cells and plasma cells do not express CD20, uncertain B cell loss is observed. Meanwhile, B cell subsets in SLE patients are normalized by rituximab [51].

Belimumab is a completely humanized monoclonal antibody that targets BLyS. Belimumab was administered subcutaneously and intravenously throughout clinical studies [52,53]. The FDA has authorized belimumab for the treatment of moderate, seropositive SLE. Belimumab has been assessed in two worldwide clinical studies [52] involving adult patients with active autoantibody-positive SLE. In addition to normal therapy, SLE patients were randomly assigned to receive either belimumab or a placebo. Both studies showed a decrease in SLE flares and disease activity, and both achieved their primary objectives. Analysis of these trials revealed that belimumab, when combined with conventional SLE treatment, improved quality of life while significantly reducing steroid use, serological activity, and rates of lupus flares [53].

Blisibimod is a substance with peptide and antibody properties that suppresses BLyS. When examined in a Phase II research study for SLE, it did not meet the SRI-5 response, which is the key effectiveness objective [54]. In SLE individuals with severe clinical symptoms, therapy was shown to be helpful, as evidenced by its ability to lower steroid usage [55]. There were no significant side effects or fatalities in the treatment groups, suggesting that the medication was well tolerated.

In patients with SLE, ocrelizumab, a completely humanized anti-CD20 monoclonal antibody, has a lesser complement-dependent cytotoxic impact and a larger antibody-dependent complement [56]. Ocrelizumab has shown promise in treating primary progressive multiple sclerosis, as well as in remitting and relapsing multiple sclerosis. Although ocrelizumab has been evaluated and shown to be effective in treating LN, it also has a high prevalence of severe infections [57].

Patients with SLE may be treated with obinutuzumab, a novel humanized glycoengineered antibody that targets CD20 type II, specifically binding to B cells [58]. *In vitro* research has demonstrated that obinutuzumab may induce greater cytotoxicity of B cells in SLE compared to rituximab. Since then, obinutuzumab has been proposed as a potential treatment option for lupus patients who are not responding to rituximab [59].

4.2 Interferon Inhibitors

Three kinds of immune-stimulatory cytokines, known as interferons (IFNs), exist: type I, type II, and type III. IFN-α is a type I IFN that has been extensively researched

Table 1. Comparison and analysis of promising markers for the diagnosis of SLE.

Markers	Research results	Future prospects
IL-8, G-CSF, IL-12/23 p40, IFN-α, TNF-α, IL-17A, IL-6, and IL-10	The highest frequencies of positive values in patients with SLE were observed for the markers: IL-12/23 p40 (52%), G-CSF (46%), and IFN-α (25%) [26].	Conducting a larger study involving male patients may create the prerequisites for developing a test system based on a comprehensive assessment of the levels of these three cytokines: IL-12/23 p40, G-CSF, and IFN-α.
IL-17, IL-6, hsCRP, complements C3, C4	Significantly higher concentrations of IL-17, IL-6, and hsCRP in patient groups compared to the control group. The opposite is true for complements C3, C4 [27]. Levels of IL-17, IL-6, and hsCRP correlated with disease severity—the SLEDAI index [26].	Complements C3, C4 can potentially be used as part of complex test systems containing other SLE markers. IL-17, IL-6, and hsCRP can potentially be used not only for general diagnostics of SLE, but also for determining the current level of the disease and further prognoses based on the dynamics of their concentrations.
PTX3	The threshold value was determined to be 2.8 ng/mL. Sensitivity was 100% and specificity was 80%. The concentration correlated with the SLEDAI index [27].	This analysis provides a ready-made prototype for a test system to diagnose SLE, determine the severity of the disease, and provide further prognosis.
BCDF	The threshold value was determined to be 98.5 pg/mL. Sensitivity was 80.6% and specificity was 70.8% [28].	A low cutoff value indicates high accuracy of the potential test system, but its development requires increasing the levels of sensitivity and specificity.
Cyr61	Serum Cyr61 levels in SLE patients were significantly higher than in healthy individuals. Sensitivity was 47% [29].	Research is needed to increase the sensitivity of the future test system.
IP-10	Sensitivity is 76% and specificity is 70% [30].	To create a test system, it is necessary to increase both the sensitivity and specificity levels.
S100A8	Correlation with the severity of LN and response to rituximab treatment, also detectable in urine and saliva [32,33].	Determining S100A8 concentrations in urine and saliva is a prerequisite for the development of simpler and more cost-effective test systems. Determination of S100A8 levels may potentially be used to predict the efficacy of monoclonal antibody therapy for SLE.
ALCAM	Correlates with SLEDAI values in patients with LN and is measured in urine [38,39].	A potentially effective marker for the diagnosis of LN.
VCAM-1	Correlates with various indicators of LN development and is detectable in urine [40,41].	A potentially effective marker for the diagnosis of LN.
PF4	When contrasted to other SLE groups, patients with active LN have the highest urinary PF4 concentrations [44].	A potentially effective marker for the diagnosis of LN.

SLE, systemic lupus erythematosus; IL, interleukin; G-CSF, granulocyte-colony stimulating factor; IFN, interferon; TNF-α, tumor necrosis factor alpha; hsCRP, high-sensitivity C-reactive protein; PTX3, pentraxin 3; BCDF, B cell differentiation factor; Cyr61, cysteine-rich angiogenic inducer 61; IP-10, interferon gamma-induced protein 10; S100A8, S100 calcium-binding protein A8; ALCAM, activated leukocyte cell adhesion molecule; VCAM-1, vascular cell adhesion molecule 1; PF4, platelet factor 4; SLEDAI, systemic lupus erythematosus disease activity index; LN, lupus nephritis.

and is widely disseminated. Several studies have examined and shown the involvement of interferons in the pathophysiology of SLE [60,61]. A Phase IIb clinical study in SLE has demonstrated the beneficial effects of sifalimumab, a completely human monoclonal antibody that targets IFN-α subtypes [60].

Patients with scleroderma have responded well to anifrolumab, a completely human immunoglobulin G1k antibody that binds to the interferon-alpha receptor (IFNAR), an antagonist of the type I interferon receptor. Anifrolumab was evaluated in SLE patients because the type I IFN reaction was comparable in scleroderma and SLE. The purpose of the MUSE study was to assess the safety and effectiveness of anifrolumab. Meanwhile, the TULIP-1 (Treatment of Uncontrolled Lupus with the Interferon Pathway-1) and TULIP-2 (Treatment of Uncontrolled Lupus with the Interferon Pathway-2) Phase III studies were subsequently performed. The FDA approved anifrolumab for the treatment of moderate to severe SLE as a result of these trials, except for patients who had central nervous system complications or LN [61].

4.3 Interleukin Inhibitors

Tocilizumab, a humanized monoclonal antibody that targets the interleukin-6 receptor, is primarily used to treat rheumatoid arthritis and giant cell arteritis. Patients who had COVID-19 have also been treated with tocilizumab. A patient with SLE who had refractory hemolytic anemia was treated with tocilizumab. A teenager with pleural effusion and SLE was also treated with it. Additionally, it has been effective in treating SLE patients who had a high fever that persisted after therapy with corticosteroids and antibiotics. It has been demonstrated that administering tocilizumab to patients with lupus who also have arthritis has positive effects. However, the use of tocilizumab in SLE is limited by the risk of neutropenia and infection [62].

A monoclonal antibody called secukinumab attaches to interleukin 17A. Secukinumab is used to treat psoriasis, psoriatic arthritis, and ankylosing spondylitis. It is believed that T-helper 17 cells have a role in the pathophysiology of SLE. A patient with psoriasis and refractory LN showed a favorable response to secukinumab treatment. The use of secukinumab in treating active LN is currently under investigation [63].

4.4 Low Dose Interleukin-2

SLE is also characterized by a loss of immune tolerance. This loss of tolerance may be caused by impaired Treg function, as well as an imbalance between T follicular helper cells and T follicular regulatory cells. Low doses of interleukin-2 in SLE patients have been shown to restore the balance between T follicular regulatory cells and T follicular helper cells, favoring T follicular regulatory cells, and demonstrate clinical efficacy in SLE [64].

4.5 Janus Kinase (JAK) Inhibitors

Rheumatoid arthritis can now be treated with baricitinib, a selective oral Janus kinase inhibitor. Patients with active SLE who were not responding to conventional therapy were assessed for baricitinib. The rash and arthritis were observed to have resolved. Nonetheless, a significant infection rate was discovered. Due to the insufficient overall efficacy, the baricitinib program for the treatment of SLE was abandoned [65]. A comparison of the therapeutic agents described above is presented in Table 2.

Monoclonal antibodies (mAbs) have the greatest potential in targeted therapy of SLE. For two approved mAbs, belimumab and anifrolumab, there is potential for expansion of use, which will enable further coverage of patients with SLE who have severe symptoms and complications. Among the mAbs under development, obinutuzumab and sifalimumab have the greatest potential for entering clinical practice within 5–10 years, having demonstrated sufficient efficacy and safety in Phase II clinical trials for the treatment of SLE.

5. Discussion

SLE is a systemic autoimmune disease that affects multiple organ systems and has a wide spectrum of clinical manifestations, from asymptomatic to severe and life-threatening consequences. The underlying pathogenesis of SLE is complex, involving numerous components at both the molecular and cellular levels. Dysfunction of the innate (e.g., neutrophils, monocytes, DCs) and adaptive (e.g., B cells and T cells) immune systems, together with genetic predisposition and influenced by environmental factors, can trigger SLE in susceptible individuals [66].

Numerous studies have demonstrated that defects in immune tolerance checkpoints—both central and peripheral—contribute to the activation of autoreactive lymphocytes and the persistence of autoantibodies. This is further aggravated by mitochondrial dysfunction, increased production of ROS, and chronic activation of pDCs, which sustain type I interferon signaling [4,67]. These mechanisms establish a self-perpetuating inflammatory loop that underlies chronic tissue damage, particularly in the kidneys, skin, and central nervous system.

From a diagnostic perspective, there is growing evidence that traditional serological markers such as ANA and anti-double-stranded DNA (dsDNA) are insufficient for reliable disease monitoring, due to their limited specificity and dynamic fluctuation. Recent studies have emphasized the importance of multiplex biomarker panels, including cytokines (e.g., IL-6, IL-17, IFN-α), chemokines (e.g., IP-10), and novel proteins (e.g., PTX3, S100A8, ALCAM), for achieving improved diagnostic precision and organ-specific disease evaluation [27,33,39,68].

Despite promising results, significant limitations remain for many of the newly proposed biomarkers for SLE,

Table 2. Comparison and analysis of promising therapeutic agents for the treatment of SLE.

Therapy tool	Target	Results	Future prospects
Rituximab (mAb)	CD20	Efficacy was shown across different types of SLE, but primary endpoints were not met.	Large Phase II trials are necessary to fully evaluate efficacy in different patient groups.
Belimumab (mAb)	BLyS	Allowed by the FDA to treat moderate SLE. Allows for a reduction in the dosage of steroid medications.	Positive results from potential studies of belimumab as mono or combination therapy in patients with severe SLE will expand the scope of this mAb in the treatment of SLE.
Blisibimod (fusion protein)	BLyS	Allows for steroid dosage reduction; however, the primary endpoints were not met in the Phase II study.	It makes sense to consider and study blisibimod in combination therapy with already approved drugs for the treatment of SLE.
Ocrelizumab (mAb)	CD20	Proven to be useful in treatment for LN patients; however, it has serious infectious side effects.	Low potential for further use due to serious side effects.
Obinutuzumab (mAb)	CD20	The primary endpoints of Phase II were met. Mild and moderate AEs.	High potential for future clinical use in the treatment of SLE, but Phase III trials are required to fully evaluate efficacy.
Sifalimumab (mAb)	IFN-α	The primary endpoints of Phase II were met. Mild and moderate AEs.	High potential for future clinical use in the treatment of SLE, but Phase III trials are required to fully evaluate efficacy.
Anifrolumab (mAb)	IFNAR	FDA approved for the treatment of moderate to severe SLE.	Positive results from potential studies of anifrolumab as a therapy for SLE patients with LN and CNS involvement will expand the scope of application of this mAb in the treatment of SLE.
Tocilizumab (mAb)	IL-6R	Single pilot studies of use in SLE. High probability of developing severe AEs.	Low potential for further exploration.
Secukinumab (mAb)	IL-17A	Single pilot studies in LN.	Full-scale clinical studies are needed to evaluate the safety and efficacy in LN.
IL-2 (protein)	T follicular cells	Pilot study shows efficacy in SLE.	Full-scale clinical studies are needed to evaluate the safety and efficacy in SLE.
Baricitinib (small molecule)	JAK kinase	Improvement in several SLE symptoms was shown, but primary endpoints were not met. High risk of developing severe AEs.	Low potential for further exploration.

BLyS, B lymphocyte stimulator; IFNAR, Interferon-alpha receptor; JAK, Janus kinase; LN, lupus nephritis; CNS, central nervous system; AEs, adverse effects; FDA, federal drug administration.

such as PTX3, S100A8, BCDF, and Cyr61, which hinder their immediate clinical implementation. These include small sample sizes in validation studies, lack of standardization in assay protocols, and insufficient specificity in distinguishing SLE from other autoimmune or inflammatory conditions [27,29,32]. Furthermore, many biomarkers demonstrate a correlation with disease activity but not with organ-specific involvement, which limits the utility of these biomarkers in targeted monitoring (e.g., LN vs. systemic flares) [26,32]. Additionally, variability between patient populations and biological fluids (serum vs. urine vs. saliva) may lead to inconsistent results [33,36]. Therefore, larger multicenter studies and the development of multiplex platforms are necessary to confirm their diagnostic and prognostic value and ensure reproducibility across diverse clinical settings [63].

Regarding therapy, while glucocorticoids and immunosuppressants remain first-line treatments, these drugs are associated with long-term toxicity and incomplete disease control. Therefore, the emergence of targeted biologics marks a transformative step in lupus care. Belimumab and anifrolumab have already received approval based on large-scale clinical trials, and other agents such as obinutuzumab, sifalimumab, and IL-2-based strategies are under investigation, with promising safety and efficacy profiles [52,60,64].

While targeted therapies, such as monoclonal antibodies (e.g., belimumab, anifrolumab, rituximab) and inhibitors of interferon or interleukin, have opened new avenues for SLE treatment, several challenges remain. These include high costs, limited accessibility in low-resource settings, and potential immunosuppressive side effects, such as infections and increased risks of malignancy [61]. Moreover, therapeutic responses vary significantly among patients, and current trials often exclude individuals with severe organ involvement, limiting generalizability. Additionally, some agents, such as blisibimod or baricitinib, failed to meet primary endpoints in clinical trials, raising concerns about efficacy and safety [54,65]. Finally, long-term safety data are still lacking for many newer biologics, necessitating extended follow-up to assess risks such as loss of efficacy, immune resistance, or cumulative toxicity [56,59].

A key direction for future research is the validation and standardization of novel biomarker-based test systems, particularly those that reflect therapeutic response or predict flares. Such tools could revolutionize the management of SLE by enabling truly personalized medicine and reducing the need for broad immunosuppression. In parallel, combination therapies that sequentially or concurrently modulate B cell, T cell, and interferon pathways may offer enhanced disease control with reduced toxicity.

In conclusion, the pathogenesis of SLE involves multifactorial immune dysregulation, which presents opportunities for the development of advanced diagnostic and therapeutic tools. Continued interdisciplinary efforts in translational immunology, clinical trials, and biomarker development will be critical for improving long-term outcomes in SLE.

6. Conclusions

During the analysis of prior research on the development of diagnostics and therapeutic agents for treating SLE, several promising options were identified. The markers that have high sensitivity and specificity indications and whose levels correspond with the severity of the disease (SLEDAI index) are the most promising. The PTX3 protein is the best choice based on these factors. Additionally, S100A8 shows potential as a biomarker of SLE, as it can be used to assess treatment efficacy. The use of two licensed monoclonal antibodies, belimumab and anifrolumab, may be expanded to include other patient groups with severe symptoms from SLE. Indeed, these antibodies demonstrated adequate effectiveness and safety in Phase II clinical trials of SLE treatment; thus, obinutuzumab and sifalimumab may become clinically available within 5–10 years among the mAbs now under development.

Abbreviations

SLE, Systemic lupus erythematosus; ANA, Antinuclear antibodies; dsDNA, Double-stranded DNA; IFN, Interferon; IL, Interleukin; TLR, Toll-like receptor; BAFF/BLyS, B cell activating factor/B lymphocyte stimulator; Th, T helper (cell); Treg, Regulatory T cell; Tfh, T follicular helper (cell); PDC, Plasmacytoid dendritic cell; ROS, Reactive oxygen species; mtDNA, Mitochondrial DNA; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; PTX3, Pentraxin 3; BCDF, B cell differentiation factor; Cyr61, Cysteine-rich angiogenic inducer 61; Gas6, Growth arrest-specific 6; IP-10, Interferon gamma-induced protein 10; VCAM-1, Vascular cell adhesion molecule 1; ALCAM, Activated leukocyte cell adhesion molecule; PF4, Platelet factor 4; LN, Lupus nephritis; mAb, Monoclonal antibody; IFNAR, Interferon-alpha receptor; IL-6R, Interleukin-6 receptor; JAK, Janus kinase; GC, Germinal center.

Author Contributions

AB and AO designed the review plan. VK, AA and OM integrated the key highlights. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Given his role as the Guest Editor, Alexander Orekhov had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Kishu Ranjan and Gustavo Caetano-Anollés.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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